REMARKS

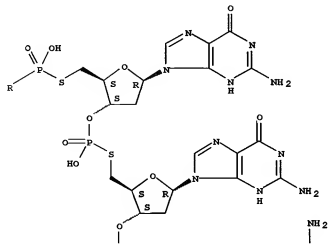
Claims 1, 4, 11-23 were pending in the instant application. The claims have not been amended.

Rejection under 35 USC § 102(b)

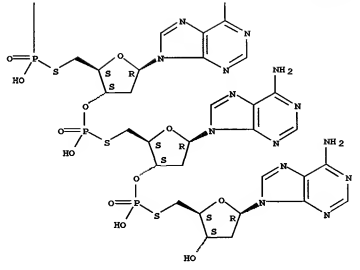
Claims 1, 11, 13, 16, 17 and 20 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Rybakov et al. The Examiner asserts that "Rybakov et al. disclose oligonucleotides having 5' thionucleotides and comprising a 5' phosphate and 3' hydroxyl, one of which is shown in the database record." Office Action at page 3. Applicants respectfully disagree that Rybakov et al. teach all of the elements of claim 1.

The oligonucleotide shown in the database record having a registry number 100242-48-6 as cited by the Examiner is reproduced below showing pages 1-A, 2-A, 3-A and 4-A, applicants note that the page 3-A is missing in the office action mailed May 14, 2008:

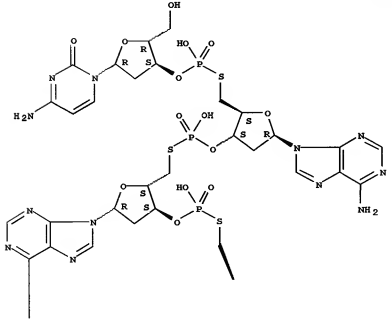
PAGE 1-A

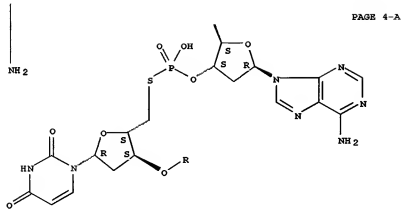


PAGE 2-A



PAGE 3-A





Applicants assert that the Examiner has misinterpreted the oligonucleotide described by the database record. The oligonucleotide described in the database record as reproduced above has the sequence 5'-CAAAUGGAAA-3', as recited in the database record, wherein the 5'-group is OH, the 3'-group is OH and each of the internucleoside linking groups is a 5'-phosphorothioate. The oligonucleotide is built in two fragments, fragment one is shown on pages 1-A and 2-A as 5'-R-P(O)OH-S-GGAAA-3'-OH and fragment two is shown on pages 3-A and 4-A as 5'-HO-CAAAU-3'-OR. When the two R groups are joined the correct sequence 5'-CAAAUGGAAA-3' is obtained which clearly has a 5'-OH group and not a 5'-thiophosphate group. Rybakov et al., therefore do not teach each and every element of claim 1. As such claim 1 and claims depending therefrom are not anticipated by Rybakov et al. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. 102(b) be withdrawn.

According to the image as shown above and as shown in the complete database record, the oligonucleotide has the following sequence reading from (5'→ 3'): 5'-R-P(O)OH-S-GGAAA-3'-OH (5'→ 3') HO-CAAAU-3'-OR and the oligonucleotide contains exclusively phosphorothioate internucleoside linkages. The oligonucleotide does not contain a 5' phosphate as the Examiner stated. Therefore, Rybakov et al. do not teach each and every element of claim 1. As such, claim 1 and the claims depending therefrom are not anticipated by Rybakov et al. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. 102(b) be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 4, 11-18 and 20 are rejected under 35 U.S.C.103(a) as allegedly being unpatentable over Uhlmann, US 6,033,909 in view of Kostenko et al., Nucleic Acids Research, 2001, 29(17), 3611-3620; Hamma et al., Biochemistry, 1999, 38, 15333-15342; and Sproat et al., Nucleic Acids Research, 1987, 15(12), 4837-4847. Applicants respectfully request reconsideration and withdrawal of the rejection because the presently claimed compositions would not have been obvious to those of ordinary skill in the art at the time of the invention.

According to the Supreme Court, a finding of obviousness requires identification of "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, 1741. The KSR Court further noted that the analysis underlying the obviousness determination "should be made explicit." *Id.* at 1741. In applying the legal principles of KSR to a case involving chemical compounds, the Federal Circuit held that "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 83 USPQ 2d 1169, 1174 (Fed. Cir. 2007) (emphasis added). As previously held by the Federal Circuit and reiterated by the KSR Court, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) (emphasis added). Applicants submit that the Examiner has failed to articulate any reason why one of ordinary skill in the art would combine elements of Uhlmann et al., Sproat et al., Kostenko et al. and Hamma et al. to produce the instantly claimed compositions.

Uhlmann et al., teach oligonucleotides having Formula I which encompass a vast genus of oligonucleotides that are defined by the specific selection of a large number of Markush variables. The Examiner asserts that it would have been obvious to one of skill in the art at the time the invention was made to produce the oligonucleotide of Uhlmann et al., having Formula I,

selecting the specific variables that provide a 5'-thiophosphate and to modify this oligonucleotide such that it further has a 3'-hydroxyl group. One of skill in the art would not have selected a 5'-thiophosphate from the disclosure of Uhlmann et al., without some further motivation as there is no teaching in Uhlmann to select the specific variables that would provide a 5'-thiophosphate.

Further, Uhlmann et al. compare DNA probes which comprise oligonucleotide analogs of Formula I to oligonucleotide derivatives with a 3'-hydroxyl group, and suggest that oligonucleotides of Formula I offer the advantage of increased nuclease stability and permit the acceptance of identical or different marker molecules at both ends of the oligonucleotide. (Uhlmann column 19, lines 31-37). In fact, in emphasizing the benefits of its DNA probes having a phosphate at the 3' terminus, Uhlmann et al. teaches away from the presently claimed invention that requires a 3'-hydroxyl group. As such one of ordinary skill in the art would not have been motivated by Uhlmann et al., to prepare oligonucleotides of Formula I with a 3'-hydroxyl group.

Kostenko et al. teach 5'-bis-pyrenylated oligonucleotides produced by conjugating pyrene to a 5' phosphorylated oligonucleotide for the purpose of producing a fluorescent probe that can quantitatively detect hybridization. (Office Action at page 5). The present claims do not encompass any oligonucleotides with a 5'-phosphate group and Kostenko et al. do not teach or suggest any oligonucleotides having a 5'-thiophosphate group.

Hamma et al. teach that producing an oligonucleotide having a 5' phosphate allows a convenient "affinity handle" for purification by strong anion exchange HPLC. (Office Action at page 6). The present claims do not encompass any oligonucleotides with a 5'-phosphate group and Hamma et al. do not teach or suggest any oligonucleotides having a 5'-thiophosphate group.

Sproat et al. teach the synthesis of 5'-S-triphenylmethyl protected nucleoside phosphoramidites. Sproat et al. also teach the preparation of 5'-(S-triphenylmethyl) mercapto-oligodeoxyribonucleotides using the 5'-S-triphenylmethyl protected nucleoside phosphoramidites. The phosphoramidite is added to an oligonucleotide to provide, after a deblocking step, a free 5'-thiol group which can be coupled to a wide variety of reagents, generating very useful probes. Sproat et al. does not teach or suggest that these phosphoramidite monomers can be substituted at any position within an oligonucleotide.

Uhlmann et al. in combination with the secondary reference do not result in the instantly claimed oligomeric compounds. Furthermore, the references fail to teach or suggest the oligomeric compounds recited in claim 1 and in fact teach away from oligonucleotides having a 5'-thiophosphate and a 3'-hydroxyl group. Sproat et al. describes the synthesis of 5'-S-triphenylmethyl protected nucleoside phosphoramidites and Kostenko et al. and Hamma et al. describe methods of preparing oligonucleotides with a 5'-phosphate group. More importantly, the cited references do not provide sufficient information to produce any oligonucleotides having a 5'-thiophosphate group as presently claimed. Accordingly, Applicants respectfully submit that the cited references, when considered individually or in combination, do not teach or suggest all the claim limitations.

The Examiner asserts that "based on the teachings of Kostenko et al., and Hamma et al., one of ordinary skill in the art recognized that synthesis of 5' phosphate oligonucleotides is routine in the art, therefore the synthesis of oligonucleotides comprising both a 5' mercapto nucleotide and a 5' phosphate is a matter of design choice made in the course of routine optimization using equivalent elements known to those of ordinary skill in the art." Applicants respectfully submit that the Examiner has failed to articulate any reason why a person of ordinary skill in the art would have combined the teachings of Uhlmann, Kostenko et al., Hamma et al., and Sproat et al., in a very particular manner to arrive at the claimed oligomeric compounds. Simply labeling an invention a "mere design choice" does not satisfy the requirement that a reason be articulated to establish obviousness. Indeed, such an assertion is exactly the sort of conclusory statement warned of by the courts. Further, there is, in fact, no reason why one of ordinary skill in the art would combine the disclosure of Uhlmann with Kostenko et al., Hamma et al., and Sproat et al., for the reasons stated above.

Even if one of skill in the art were to combine Uhlmann et al., Sproat et al., Kostenko et al. and Hamma et al., despite lacking guidance to produce a 5'-thiosphosphate group, there would be no specific reasoning or teaching provided to one of ordinary skill in the art to modify the oligonucleotides disclosed by Uhlmann et al. to arrive at the claimed invention. Accordingly, none of the cited references describe or suggest compositions comprising oligomeric compounds

that have the claimed substitution pattern of chemical modifications, and there is no reason why those of ordinary skill in the art would have produced oligomeric compounds having the particular substitution pattern of claimed modifications e.g., 5'-thiophosphate and 3'-hydroxyl, prior to applicant's invention.

Also as explained above, the combination of Uhlmann et al. with the secondary references cannot be made in further view of the negative teachings of Uhlmann et al. with regard to having a 3'-hydroxyl terminus. Uhlmann teach away from the oligonucleotides with a 3'-hydroxyl group. (Uhlmann column 19, lines 31-37). There is nothing in either Kostenko et al. or Hamma et al. to assist in overcoming this negative teaching about the oligonucleotides with a 3'-hydroxyl group. Although Sproat et al. describe the synthesis of 3'-hydroxyl protected nucleosides, this combination would not have motivated one of skill in the art to make or modify Uhlmann's oligonucleotides to meet the requirements of Applicants' claims. In fact, the person of skill in the art would likely draw the opposite conclusion. The claimed oligomeric compounds would therefore not have been obvious to those of ordinary skill in the art at the time of the invention, and applicants accordingly, respectfully, request withdrawal of the rejection for alleged obviousness.

Applicants believe the foregoing constitutes a complete response to the Office Action and submit that all pending claims are in condition for allowance. It is believed that no fee is due, however, the Commissioner is authorized to charge any additional fees to Deposit Account 50-0252, referencing docket number ISIS-5582.

Respectfully submitted,

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